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# THE VACCINE THERAPY OF GONOCOCCAL INFECTIONS

Based upon an Address delivered before the Medical Society for the Study of Venereal Diseases on February 27th, 1925, by Prof. J. W. H. EYRE, M.D., M.S., D.P.H.

MR. PRESIDENT AND GENTLEMEN :

In opening the discussion this evening on the vaccine therapy of gonorrhœa, may I at once express my appreciation of the honour your Council has done me in asking me to perform this function and, at the same time, express some of the diffidence I, as a laboratory worker in the main, feel in addressing a body of men all of whom have much closer clinical acquaintance with the disease than I have.

I must not, however, attempt to plead ignorance of the clinical aspects of gonococcal infections, since, thanks to the kindness of my colleagues and my close contact with the V.D. Clinic at Guy's, I am more or less familiar with the disease and its complications, and take a lively interest in the difficulties that confront the specialist in its treatment.

In this connection, may I refer for a moment to the address delivered last month by our President, and fervently reiterate his hope that the clinician will cultivate the habit of taking his troubles and difficulties to the laboratory and discussing them with his colleague, the pathologist.

For the tendency to-day is in the direction of specialisation *in excelsis*, and the worker who is occupied all the time, or most of the time, in the treatment of a particular disease is in danger of finding his horizon considerably contracted, with a consequent loss of perspective, whilst the pathologist, on the other hand, whose services are requisitioned by all and sundry of his colleagues—physicians, surgeons, and specialists in every branch of medicine and surgery—is compelled perforce to take a very broad view of infection as a whole, and, by his experiences of the remoter effects of an infection resulting from any given micro-organism as they intrude themselves

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in otherwise unassociated symptom complexes, is likely to be able to give just that odd fact or piece of information the particular specialist is looking for.

To come to the particular subject in hand, I make no apology for the fact that my contribution to the discussion is not based upon experiments carried out specifically for that purpose, and I take it that you would prefer that I should deal rather with general principles and opinions based upon a somewhat varied experience in the use of vaccines.

### GENERAL CONSIDERATIONS

In the first place, I would suggest that present-day vaccine therapy is an immature and imperfect attempt on the part of mere humans to imitate the reparative methods of Dame Nature. It is necessarily imperfect by reason of our profound ignorance of the very fundamentals of Nature's methods, whilst its immaturity is shown by the many modifications that it has undergone since it was first practised a quarter of a century ago.

Our conception of immunity to infection and the cure of disease has varied from time to time, as shown by the elaboration of innumerable theories, ranging from the purely "humoral" of Pasteur and the purely "cellular" of Metchnikoff to the combined "serum and cell" doctrine of Wright and Leishman, which is most favoured to-day. But the majority have postulated the existence in the circulating fluids of the infected and the convalescent of several hypothetical substances, all grouped under the generic term "anti-body," which includes anti-toxins, immune bodies, agglutinins, etc., all individually highly specific, in addition to bodies of similar functions present in the blood plasma of all, whether normal or infected or convalescent, and known as complement and opsonin; and it is morally certain that many others will be added to the list ere the tale of anti-bodies is complete.

But although the wit of man has devised methods by which many different types of anti-body may be demonstrated to the physical senses, their correct orientation is still a matter of conjecture. We do not know whether, for instance, immune body or agglutinin is the more important factor in the production of immunity, or, indeed, whether either fulfil any useful function.

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At the same time, it is probably accurate to state that the various anti-bodies that are capable of recognition gradually increase in amount, though usually with many fluctuations, in the blood serum of an infected individual progressing towards immunity, and that the curves representing these amounts roughly, but only very roughly, correspond. The estimation of their relative amounts does, however, afford an index of the activity of the immunising machinery, and in this sense subserves a very useful purpose.

The phenomenon thus outlined can be reproduced in the laboratory by inoculating into a selected laboratory animal cultures of some pathogenic bacterium, either in the living state, when in some cases it may be necessary to resort to various expedients to attenuate its virulence, or "dead" as the result of the action of some chemical or physical reagent; and, further, by intentional variations in the amount or virulence of our "antigen" in relation to the anti-body content of the serum and the activity of the tissue cells—in other words, by varying the interactions between the "seed" on the one hand, and the "soil" on the other—we can reproduce those fluctuations already referred to.

Finally, the extent of the immunity ultimately attained can be estimated in terms of massive doses of the antigen which, when introduced into the prepared animal, fail to produce any demonstrable pathological lesion.

This being so, it is only fair to assume that our present-day conception of the course of events when an infected individual is putting up a sufficiently successful fight against the invading bacteria to enable him to progress steadily towards convalescence, is a sufficiently good working hypothesis to guide us in the use of vaccine in treatment; and although it is the fashion (and after all, there are fashions in pathology as well as in clinical medicine) to decry the hypothetical body "opsonin" and all the theories that some twenty years ago were built upon the movements of the opsonic index, still it must be remembered that much of our present-day work is built upon some such basis. I make, therefore, no apology for referring to the curve representing an opsonic cycle; I would merely remark that for all practical purposes it would represent the movements of a specific agglutinin or immune body, or any other known anti-body,

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equally well, and shows the alterations that would take place in the corresponding anti-body content of the serum as the result of a single injection of an efficient antigen, *viz.*, first a fall in demonstrable anti-body (the so-called "negative phase") extending usually over a comparatively short period followed by a more or less marked rise (corresponding to the "positive phase") this high-water mark being maintained in a position of equilibrium for a variable period according to the intensity of the response evoked by the antigen before "declining" towards the original level. In natural infections the probability is that the individual receives successive auto-inoculations—the result of each of which, in favourable cases, would be represented by this particular curve—but the sequence of stimuli converts this single experiment curve into the gradual ascent shown in a previous slide. It is our object, therefore, in dealing with vaccines, to so arrange our doses as to size and time of introduction into the economy as to create a sequence of favourable curves which will merge naturally into a curve representing the building up of a big reserve of anti-body.

### TISSUE RESISTANCE TO GONOCOCCAL INFECTION

In most instances, recovery from an infection of bacterial origin is followed by a longer or shorter interval during which the individual is insusceptible to a further infection with the same bacterium; in other words, there is a period of immunity, and specific anti-bodies can be demonstrated in serum. In some cases, such as typhoid, this period of immunity lasts for years, perhaps for life; with others, as for example, gonorrhoea, the period of immunity is quite short.

Again, possibly in consequence of the transmission of traces of specific anti-bodies from ancestors who have suffered and recovered from various infections the normal individual appears to possess in some degree the power of resisting the invasion of his tissues by most pathogenic bacteria, and laboratory observations have demonstrated the existence of definite bactericidal powers in the serum and other body fluids; presumably it is this fact that enables him to put up a strenuous resistance to most of the pathogenic organisms. But this power fails to function when brought into relation with, at any rate,

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two organisms, *viz.*, the specific agents of Mediterranean fever and of gonorrhœa.

With the first of these we are not at present concerned, but on account of this lack of resistance to the gonococcus especial care is needed in the employment of vaccine therapy, since it is exceedingly easy to sensitise even the normal individual to the gonococcus, and I have seen instances where even small doses of vaccine, when introduced subcutaneously, have led to the formation of small localised areas of necrosis and to the formation of small nodules, the contents of which, on incision, have proved to be sterile pus.

### TYPES OF GONOCOCCI

At your last meeting Dr. Renshaw, in his *résumé* of previous work on the subject of vaccine therapy, reminded you that, for example, Torrey, who had isolated and studied carefully a number of different strains of gonococci, was of opinion that from the antigenic point of view they are by no means identical.

He at first described six groups or types, subsequently increased these to ten, and, I believe, now, like Watabiki and Hermaines, is ready to believe that every strain of gonococcus isolated from the human subject forms an antigenic species by itself. This attitude is, I think, the one to which we are all forced sooner or later. Certain it is that serological reactions, such as cross agglutinations, absorptions, and so on, do suggest the existence of a multiplicity of types. On the other hand, morphologically and culturally the gonococcus, whatever its source, gives consistent reactions.

This diversity of type, as shown by serological tests, is so striking that I have long ceased to regard it with surprise, believing that the environmental conditions are responsible for the serum diversities of the strains.

My own work, however, has forced upon me the suggestion that there are three main varieties of the gonococcus. The first of these is the type of gonococcus obtained from the conjunctival sac, not only in cases of ophthalmia neonatorum, but in cases of gonorrhœal conjunctivitis occurring in the adult. This is a type which, as a rule, is the least parasitic ; it grows fairly readily and does not present much difficulty in isolation, but does not appear

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to have the same antigenic value when converted into a vaccine and employed in the treatment of other than ocular lesions as has either of the two remaining types.

The next type is that isolated from the joint fluid in cases of gonorrhœal arthritis. This is less saprophytic than the ocular type, and less parasitic than my third type. It, also, can be isolated readily and grows fairly well, although not so luxuriantly as that from the eye. It is, however, a fairly good antigen for all varieties of gonorrhœal lesions.

The third type is that isolated from acute "genital" gonorrhœa, whether male or female. This type is certainly the most highly parasitic, requires greater care in its isolation and cultivation than either of the other two, and, on the whole, is of very considerable antigenic value; but amongst the gonococci isolated from this situation one encounters the greatest number of serological differences.

### GONOCOCCUS VACCINES

From what has already been said as to the lack of antigenic uniformity in the various strains of gonococci, it is quite clear that an autogenous vaccine is much to be preferred whenever its preparation is possible.

A young culture of the organism—as few laboratory generations as possible distant from the human body—makes the best vaccine. At the same time it is the most toxic, and probably owes its value to the fact that its bioplasm has undergone the least modification. Elsewhere I have insisted upon the importance of this point, a point which, I think, explains the necessity for the enormous dosage that is sometimes advised with stock vaccines, prepared, as these often are, from cultures which have been kept going in the laboratory for countless generations. Their antigenic value is, in my experience, far inferior to the freshly isolated organism, so much so that I believe that the size of the dose needed to provoke a definite immunising response increases directly with the number of generations the organism is removed from the body.

But often it is well-nigh impossible to obtain an autogenous vaccine, owing to inherent difficulties in obtaining the gonococcus from the infected individual. That being

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so, it is very comforting to know that a stock vaccine prepared from a number of different strains is of considerable value, and one would certainly recommend the use of a stock vaccine rather than no vaccine at all.

In the selection of strains for the preparation of a polyvalent stock vaccine, those should be employed which have already, as autogenous vaccines, proved their antigenic value.

At one time the use of sensitised gonococcus vaccine was strongly urged. For the preparation of these vaccines it is necessary to have on hand an immune serum containing a sufficiency of specific anti-body of the nature of amboceptor (or immune body) to sensitise the gonococcus. But in view of the multiplicity of serological types previously referred to, it is clear that to obtain thorough sensitisation a separate serum must be used for each strain comprised in the polyvalent vaccine—a matter of considerable difficulty; and when I recall that sensitised gonococcus vaccines were amongst the earliest used in this country, and that the sensitisation was believed to be effected by the use of a commercial anti-gonococcus serum, it is easy to realise why the use of the so-called “sensitised” gonococcus vaccine rapidly faded away.

A sensitised autogenous vaccine is hardly within the bounds of routine work; by the time an immune serum has been prepared—often a matter of some weeks—the individual patient for whom it is required has either recovered completely or has passed into other hands for treatment.

Much has been made recently of detoxicated vaccines, which to many workers means that the bacterial protoplasm has been altered by a preliminary treatment with acids, alkalis, or other chemical reagents in the attempt to remove from it some fraction of the protein molecule which appears to these observers to be unnecessary to the production of immunity.

With such vaccines, however, I have been unable to satisfy myself that, when injected into experimental animals, they have stimulated the formation of any appreciable quantity of anti-body coming under the category of those already mentioned as demonstrable by laboratory tests; and I have come to regard vaccines of this kind merely in the light of indifferent vegetable proteins, and the effects they produce to depend upon the

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little understood "protein shock." True detoxication, in the sense that I understand it, implies, as I have said elsewhere, that the power of toxin formation has been diminished or abolished by prolonged laboratory culture under carefully adjusted conditions, and has only been attained in connection with a few bacteria, notably by Pasteur, who, years ago, elaborated a detoxicated vaccine of *Bacillus anthracis* which has proved eminently successful in use. So far as autogenous vaccines are concerned, however, this class of detoxicated vaccine is at present outside the range of practical therapy.

### PROTEIN SHOCK

There is another aspect of the treatment of gonococcus infections which may well be referred to here. As Dr. Renshaw and the President have reminded you, typhoid vaccine and plague prophylactic have both been used for this purpose. Indeed, typhoid vaccine has often produced very striking results in cases of gonorrhœal arthritis. Solutions of blood or meat peptone, and also milk, have similarly been employed. But with all these reagents, which are usually injected intravenously, one depends upon the vaso-motor shock, the attendant pyrexia, and the subsequent leucocytosis to so stimulate the reparative processes of the body as to obtain an amelioration of the condition under treatment ; but we are not yet really in a position to formulate any theory which will adequately and easily explain the reaction that takes place in response to the introduction of a foreign protein into the circulation, and we are still groping in the dark in our endeavour to control the forces that are liberated by these procedures.

### THE EMPLOYMENT OF VACCINES IN GONORRHŒAL INFECTIONS

Some years ago, in conjunction with my friend Dr. Stewart, the effect of gonococcus vaccine was studied in a number of hospital cases placed at our disposal by our colleagues, and in which we were able to follow the results of treatment under exceptionally favourable conditions ; and the opinions we then formed and the conclusions we came to appear to me as much justified to-day as they did then. First of all, attention to the personal equation. It must be recognised that the human subject does not



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respond to the introduction of a vaccine into his body in exactly the same way that a guinea-pig or a rabbit does ; nor does one patient respond in exactly the same way as another. The pathologist, having supplied what he honestly believes to be the best vaccine for the purpose, can only indicate on very broad lines the doses which should be employed. To be successful, vaccine therapy entails a careful study of each and every individual case ; and, as I have previously remarked, just as fluctuations in the anti-body content of the serum can be shown to follow variations in dosage, so clinical symptoms can be observed in the patient which indicate to the clinician the progress of the infection. Thus, with a urethritis, the introduction of a dose of vaccine is usually followed within a few hours by an increase in the amount of discharge and microscopically by the presence therein of a larger number of gonococci. If the dose was too large, this " negative phase," as it is called, may last for many days and recovery only slowly takes place. If the dose was correct, some twelve or eighteen hours later the discharge has diminished in amount, gonococci are noticeably fewer in number, and this improvement continues fairly steadily. If the dose was too small no alteration in the clinical symptoms are observable. Again, if the dose is much too large constitutional symptoms attended by pyrexia may occur, a danger signal that cannot be disregarded.

In acute cases doses of vaccine should be small, even *very* small, say half a million gonococci, and these small doses should be repeated at intervals of not less than four or five days. Doses may be gradually increased in size as time goes on, and when doses of, say, five millions are reached, the injections should not be made at more frequent intervals than once a week. Still increasing the dosage, when ten or fifteen millions are reached, then the injections should be made at not closer intervals than twelve or fourteen days. Such suggestions refer to auto-genous vaccines. With a potent stock vaccine, prepared from young and virulent cultures, a similar sort of dosage would hold good ; but where, from one circumstance or another, the vaccine has had to be compounded from strains that have been under laboratory cultivation for any period of time, although then the initial dose should still be small, the increments may be considerably greater than those mentioned above, so that, in the course of

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treatment, one may arrive at doses of fifty, seventy-five or even one hundred millions.

In early acute and in chronic infections, where the gonococcus is the only organism involved, there is no object, to my mind, in using other than pure gonococcus vaccines; but, as is common knowledge, in a large number of instances the gonococcus, by reducing the vitality of the tissues at the site of infection, paves the way for the entrance of organisms which were previously simply saprophytic, but which are now enabled to obtain a foothold and to become pathogenic; in this way, for example, even the staphylococcus—ordinarily a normal saprophyte in the genito-urinary tract—can become an infecting agent. In cases such as these the use of mixed vaccine, in which the staphylococcus forms a definite part, is often advocated; and the combined gonococcus and syncoccus vaccine of the French workers is an illustration of a stock vaccine adapted to meet this contingency. Personally, when such cases occur, I much prefer to employ two separate vaccines, one of the gonococcus and a separate one of the associated organism, whatever it may be; and whilst treating the two infections simultaneously, treat them as distinct infections.

A digression may be permitted me here in my search for information. Besredka's work on the local immunisation of definite groups of cells is attracting considerable attention; and in the case of blepharitis with infection of the meibomian ducts with the staphylococcus (usually *albus*) one certainly does obtain better results in treatment if, in addition to an autogenous vaccine and the regular expression of the purulent material from the meibomian ducts, the lids are bandaged once or twice a week for a period of twenty minutes at a time with lint saturated with the same autogenous vaccine; and I should be interested to hear of the experiences of others present who have employed gonococcus vaccine in the attempt to obtain locally similar tissue reactions.

There is one other point to which I hardly like to refer in such a meeting as this, namely, accuracy in diagnosis. At the present time it is hardly too much to say that no clinician completes his diagnosis without the aid of the microscope; but it has not always been so, and the fact remains that other organisms—such as the *Streptococcus pyogenes longus*, the pneumococcus, the staphylococcus

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(both *albus* and *aureus*), the *Bacillus coli*, the pneumobacillus of Friedlander—may each and all, on occasion, give rise to an acute purulent exudate clinically indistinguishable from that due to the diplococcus of Neisser ; and, most troublesome of all, I have met with cases of juvenile vulvo-vaginitis where the responsible organism has not been the gonococcus, but the *Micrococcus catarrhalis*. Luckily, these are rare ; but it is obvious that in none of these infections could a gonococcus vaccine be expected to produce any specific improvement.

Finally, if one were allowed to select cases with a view to demonstrating the value of vaccine treatment, one would naturally choose the earliest and the most acute gonorrhœas, rather than chronic ones ; these cases, to my mind, respond most readily and most completely to vaccine therapy. Next, gonorrhœal arthritis, as being profoundly influenced by vaccine therapy. And next, the cases of gonorrhœal iritis and irido-cyclitis.